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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/234,733	01/21/1999	MIN JIANG	9000-0030.10	5673

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EXAMINER
HINES, JANA A

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No. 09/234,733	Applicant(s) JIANG ET AL.	
	Examiner Ja-Na A Hines	Art Unit 1645	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 16 April 2002 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *16 April 2002*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See attached response*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☐ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *None*.

Claim(s) objected to: *None*.

Claim(s) rejected: *1-12,44 and 45*.

Claim(s) withdrawn from consideration: *None*.

Advisory Action

Withdrawal of Rejections

1. The rejection of claims 1-12, 44, 46, 49, 52 and 55 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention is withdrawn in view of applicants inventions.

2. The rejection of claims 1-12 and 44-55 under 35 U.S.C. 112, second paragraph is withdrawn in view of applicant's amendments and arguments.

Response to Arguments

3. Applicant's arguments filed April 16, 2002 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The rejection of claims 1-12 and 44-55 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule comprising SEQ ID NO:1 which encodes the amino acid sequence of SEQ ID NO:2

a polypeptide having at least 90% sequence identity to amino acid positions 1-256 or 29-256 is maintained because such amendments do not overcome the rejections.

Applicants assert that the test for enablement is whether one skilled in the art could make use of the claimed invention from the disclosure without undue experimentation and that the specification need only set forth information as is sufficient to allow one of ordinary skill in the art make and use the invention and how such a teaching is accomplished either by the use of illustrative examples or by broad terminology is of no importance since a specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph requirements unless there is reason to doubt the objective truth of the statements relied upon.

However, the art teaches that replacement of a single amino acid residue may lead to both structural and functional changes in the biological activity of a protein. One of skill in the art would be reduced to merely randomly altering amino acids which would lead to unpredictable results regarding the functional activity of the immunogenic polypeptide. The art is replete with examples that even one amino acid change can lead to unpredictable changes in the biological activity of the protein, as stated in the previous office action. See also, Jobling et al., (1991) which teach a panel of single amino acid substitutions by oligonucleotide directed mutagenesis produces protein that differ in native conformation, immunological recognition, binding and toxicity, thus

immunological recognition. Applicants have not taught which residues of SEQ ID NO:

or 5 can be varied and still achieve the desired polypeptide. Also, it is noted that if one nucleotide is deleted or inserted at a single place within the coding sequence, all codons down stream if that insertion or deletion will be frame shifted; thus it is highly likely that the protein expressed will have little in common structurally or functionally with the instant polypeptide.

Applicants claim that the instant claims meet the test for enablement in view of the disclosures providing considerable direction and guidance on how to practice their invention and present working examples, thus one skilled in the at could identify the claimed immunogenic polypeptides using routine experimentation. However, the skilled artisan would have to discover what the appropriate additions, deletion and substitutions could be. This experimentation would require inventiveness beyond that expected skilled artisan. To the contrary of applicants' assertions, the specification fails to provide guidance on how any amino acid can be substituted or inserted for the production of a polypeptide nor does the specification provide guidance on how any location can be used to produce a stable polypeptide. There is no recitation of specific locations for deletions, substitutions, or insertions. In this regard, applicant has not enabled the scope of the invention as claimed for those amino acid sequences having at least 90% identity. Therefore, such undisclosed and unidentified amino acid and sequences, which result from insertions, deletions, or substitutions encompassed by the recited 90% identity, are not enabled for their scope.

constitute undue experimentation, and that the stated art does not state that undue

experimentation would be required to determine whether or not the protein was stable and has the desired biological activity. However, applicants have not taught which residues of the sequence can be varied and still achieve a functional protein. There is no teaching of an immunogenic polypeptide having 90% sequence identity to SEQ ID NO:5. The specification has not conceived of any other functionally equivalent polypeptides or sequences encoding an immunogenic polypeptide, there is no teaching of general tolerance to substitutions or where substitutions could be made. Thus the specification fails to enable the skilled artisan to envision the detailed chemical structure of the claimed structure of the claimed polypeptide. The skilled artisan would be forced into undue experimentation to make and use the instantly claimed invention. In this case 10% of the amino acids can be modified with one of 22 different amino acids, wherein the amino acids to be substituted are within any location within the sequence, thus thousands of different polypeptides could be made by substituting only a single amino acid position, thus the number of claimed sequences is potentially enormous. Such experimentation is clearly more then routine and would be undue, and one of skill in the art would have to identity locations and specific substitutions within the sequence to produced the claimed immunogenic polypeptide. Therefore such undisclosed and unidentified amino acids, which result from these insertions, deletions or substitutions encompassed by the recited sequence having at least 90% sequence identity, are not enabled for their scope.

considerable direction and guidance on how to practice their invention. Thus, the skill

in the art could identity the claimed immunogenic polypeptides using routine experimentation, thereby meeting the requirements for enablement.

However, in this case, the skilled artisan would have to discover de novo what the appropriate additions, deletion and substitutions would be. Such experimentation requires ingenuity beyond that expected of one of ordinary skill in the art. Such need for non-routine experimentation demonstrates that the specification is not enabled for any asserted use or well-established use of a sequence encoding an immunogenic polypeptide having at least 90% identity to SEQ ID NO:2 or 5. The additions/deletions, substitutions or insertions of any amino acid in any location within the polypeptide would not predictably result in a claimed polypeptide. It is well known in the art that certain positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spacial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. The specification does not provide guidance on how any amino acid can be substituted or inserted for the production of a polypeptide nor does the specification provide guidance on how any location can be used to produce a stable polypeptide. The specification broadly teaches sequence identity to include additions/deletions, substitutions or insertions, therefore any modified polypeptide is being claimed with no recitation of specific locations for deletions, substitutions, insertions or any combination. Applicants cannot simply predict what

has not enabled the scope of the invention as claimed for those amino acid sequences

having at least 90% identity. Therefore, such undisclosed and unidentified amino acid and sequences, which result from insertions, deletions, or substitutions encompassed by the recited 90% identity, are not enabled for their scope. No working examples are shown containing a representative sequence having at least 90% sequence identity which would thereby contain the missing information. Without such information, one of skill in the art could not predict which deletions, substitutions or insertions or any combination would result in the desired polypeptide. Accordingly, one of skill in the art would be required to perform undue experimentation to use any amino acid at any location to produce such polypeptides. Therefore, one skilled in the art could not make and/or use the invention without undue experimentation.

Applicant sets forth that Brenner et al., has determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over a at least 150 residues and that using sequence comparison methods is well-defined in the art and that the degree of relatedness had been previously determined by sequence comparisons; thus one of skill in the art would expect to be able to use generally applicable methods for sequence comparison methods. However, the sequence comparison methods are not the issue, but rather the lack of teaching for how to make an immunogenic polypeptide having at least 90% sequence identity to SEQ ID NO:2 or 5. As stated above, there is no teaching of any other functionally equivalent polypeptides or sequences encoding an immunogenic polypeptide, there is

therefore the specification fails to enable the skilled artisan to envision the detailed

chemical structure of the claimed structure of the claimed polypeptide and a skilled artisan would be forced into undue experimentation to make and use the instantly claimed invention. Moreover, Brenner et al., does not provide the missing information. Brenner et al., is using a dataset of proteins with known structural and functional relationships and determining the evolutionary homology between them. This, is unlike applicants claims that require an artisan to de novo discover and create another polypeptide having at least 90% sequence identity. Brenner et al., does not teach which amino acids substitutions, additions or deletions to use in order to create a polypeptide sequence having the claimed functions. Brenner et al., does not teach which regions will or will not tolerate such changes. Therefore Brenner et al., is not commensurate in scope with the instant claims. Neither does the article teach what the appropriate amino acid changes should be without causing detrimental effects to a polypeptide being produced. Therefore, the article is not persuasive.

Finally, applicants argue that the SEQ ID NO:2 has 265 amino acids and SEQ ID NO:5 has 227 amino acids and a sequence having at least 90% sequence identity to the contiguous amino acid sequences of SEQ ID NO:2 or 5 well exceeds the statistical threshold required for reliable prediction of homology and that in consideration of the evidence and reasoning presented by applicant one of ordinary skill in the art would reasonably expect that the polypeptide of the invention would more likely than not possess the function of a SEQ ID NO:2 or 5. However, stated above, the instant claims

appropriate additions, deletion and substitutions could be and such experimentation

would require inventiveness beyond that expected of a skilled artisan; and in view of a specification which fails to provide guidance on how any amino acid can be substituted or inserted for the production of an immunogenic polypeptide and guidance on critical locations which cannot tolerate modifications, thereby allowing one to produce an immunogenic polypeptide having at least 90% sequence identity to SEQ ID NO: 2 or 5 without performing undue experimentation to achieve such results, the instant claims are not enabled and the rejection is maintained.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is (703) 305-0487. The examiner can normally be reached on Monday through Thursday from 6:30am to 4:00pm. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Ja-Na Hines JH
May 31, 2002

PATRICIA A. DUFFY
PRIMARY EXAMINER